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Dual blockade of EGFR and CDK4/6 delays head and neck squamous cell carcinoma progression by inducing metabolic rewiring

Sanjib Chaudhary[a], Ramesh Pothuraju[a], Satyanarayana Rachagani[a], Jawed A. Siddiqui[a], Pranita Atri[a], Kavita Mallya[a], Mohd W. Nasser[a, i], Zafar Sayed[b], Elizabeth R. Lyden[c], Lynette Smith[c], Siddhartha D. Gupta[d], Ranju Ralhan[e, f], Imayavaramban Lakshmanan[a], Dwight T. Jones[b], Apar Kishor Ganti[g, hj, **], Muzafar A. Macha[i, ***], Surinder K. Batra[a, jk, *]

[a] Department of Biochemistry and Molecular Biology, USA
[b] Department of Otolaryngology-Head & Neck Surgery, USA
[c] Department of Biostatistics, University of Nebraska Medical Center, Omaha, NE, 68198, USA
[d] Department of Pathology, All India Institute of Medical Sciences, New Delhi, India
[e] Department of Otolaryngology-Head & Neck Surgery, Mount Sinai Hospital, Toronto, USA
[f] Department of Internal Medicine, USA
[g] VA Nebraska Western Iowa Health Care System, USA
[h] Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE, 68198, USA
[i] Watson-Crick Center for Molecular Medicine, Islamic University of Science and Technology, Awantipora, Jammu and Kashmir, 192122, India
[j] Fred and Pamela Buffett Cancer Center, USA
[k] Eppley Institute for Research in Cancer and Allied Diseases, University of Nebraska Medical Center, Omaha, NE, 68198, USA

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ABSTRACT

Despite preclinical success, monotherapies targeting EGFR or cyclin D1-CDK4/6 in Head and Neck squamous cell carcinoma (HNSCC) have shown a limited clinical outcome. Here, we aimed to determine the combined effect of palbociclib (CDK4/6) and afatinib (panEGFR) inhibitors as an effective strategy to target HNSCC. Using the TCGA-HNSCC co-expression analysis, we found that patients with high EGFR and cyclin D1 expression showed enrichment of gene clusters associated with cell-growth, glycolysis, and epithelial to mesenchymal transition processes. Phosphorylated S6 (p-S6), a downstream effector of EGFR and cyclin D1-CDK4/6 signalling, showed a progressive increase from normal oral tissues to leukoplakia and frank malignancy with poor outcome. While increased p-S6 level was drastically reduced during combination treatment in the HNSCC cell lines and mouse models. Combination treatment reduced the cell growth and induced senescence via increasing reactive oxygen species with concurrent ablation of glycolytic and tricarboxylic acid cycle intermediates. Additionally sub-cutaneous and genetically engineered mouse model (K14-CreER^{tam};LSL-Kras^{G12D};Trp53^{R172H}) studies indicated reduction in the tumor growth and delayed tumor progression, respectively. This study collectively demonstrates that dual targeting may be a critical therapeutic strategy in blocking tumor progression via inducing metabolic alteration and warrants clinical evaluation.

1. Introduction

Overexpression or hyperactivation of epidermal growth factor receptor (EGFR) [1–4], cyclin D1 [5,6] along with simultaneous low levels of cyclin-dependent kinase inhibitor 2A (CDKN2A or p16Ink4a) [7] are the hallmarks of various cancer types, including a majority of head and neck squamous cell carcinoma (HNSCC). This dysregulation is associated with resistance to chemo-radiation therapy (CRT), promotes disease recurrence, and poor prognosis in the HNSCC patients [8,9]. Despite recent advances in the different treatment modalities in HN-

* Corresponding author. University of Nebraska Medical Center, Omaha, NE, 68198-5870, USA.
** Corresponding author. University of Nebraska Medical Center, Omaha, NE, 68198-5870, USA.
*** Corresponding author. Watson-Crick Center for Molecular Medicine, Islamic University of Science and Technology, Awantipora, Jammu and Kashmir, 192122, India.
E-mail addresses: aganti@unmc.edu (A.K. Ganti), muzafar.aiiims@gmail.com (M.A. Macha), sbatra@unmc.edu (S.K. Batra).

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